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Superiority of Hypertonic Saline/Dextran Over Hypertonic Saline During the First 30 Minutes of Resuscitation Following Hemorrhagic Hypotension in Conscious Swine

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DIVISION OF MILITARY TRAUMA RESEARCH

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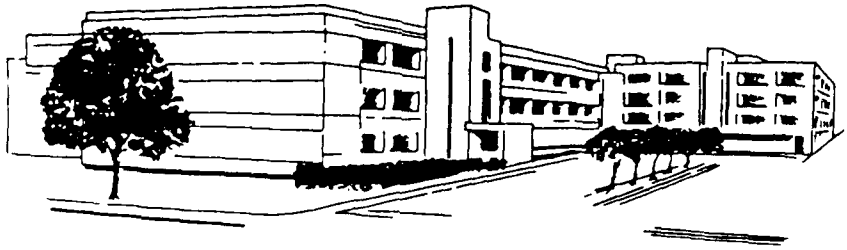

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We compared the effectiveness of intravenous administration of hypertonic saline/dextran (7.5% NaCl in 6% Dextran-70, n=6) to hypertonic saline alone (7.5% NaCl, n=8) in rectifying the detrimental effects of hemorrhage on cardiovascular function. Chronically instrumented conscious swine were hemorrhaged 37.5 ml/kg over 60 min in an exponential manner. If untreated, this model is 100% lethal within 60 min of hemorrhage completion. Immediately after hemorrhage, the swine were administered hypertonic saline/dextran or hypertonic saline at 4 ml/kg, and functional variables were measured before and at 5, 15, and 30 min following treatment. Hypertonic saline/dextran produced a significantly greater plasma volume expansion than hypertonic saline alone (13.6 compared to 9.9 ml/kg). This expansion, furthermore, was sustained in pigs receiving HSD, but regressed over 30 min in pigs receiving HS. In both treatments the cardiac index was

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increased, but to a greater extent with HSD, 104 ml/kg/min, compared to HS alone, 46 ml/kg/min. Over the 30-min post-treatment period, these initially elevated values were not fully sustained in either group, but remained consistently greater than the values recorded at the end of hemorrhage; however, the difference in cardiac index between treatments was maintained during this period. Oxygen delivery showed a trend similar to that of cardiac index, with HSD producing a greater improvement and the difference between groups again sustained over the 30 min. We conclude that resuscitation with HSD is superior to that of HS in improving cardiovascular function over the first 30 min after hemorrhage.

ABSTRACT

We compared the effectiveness of intravenous administration of hypertonic saline/dextran (7.5% NaCl in 6% Dextran-70, n=6) to hypertonic saline alone (7.5% NaCl, n=8) in rectifying the detrimental effects of hemorrnage on cardiovascular function. Chronically instrumented conscious swine were hemorrhaged 37.5 ml/kg over 60 min in an exponential manner. If untreated, this model is 100% lethal within 60 min of hemorrhage completion. Immediately after hemorrhage, the swine were administered hypertonic saline/dextran or hypertonic saline at 4 ml/kg, and functional variables were measured before and at 5, 15, and 30 min following treatment. Hypertonic saline/dextran produced a significantly greater plasma volume expansion than hypertonic saline alone (13.6 compared to 9.9 ml/kg). This expansion, furthermore, was sustained in pigs receiving HSD, but regressed over 30 min in pigs receiving HS. In both treatments the cardiac index was increased, but to a greater extent with HSD, 104 ml/kg/min, compared to HS alone, 46 ml/kg/min. Over the 30-min post-treatment period, these initially elevated values were not fully sustained in either group, but remained consistently greater than the values recorded at the end of hemorrhage; however, the difference in cardiac index between treatments was maintained during this period. Oxygen delivery showed a trend similar to that of cardiac index, with HSD producing a greater improvement and the difference between groups again sustained over the 30 min. We conclude that resuscitation with HSD is superior to that of HS in improving cardiovascular function over the first 30 min after hemorrhage.

Superiority of Hypertonic Saline/Dextran Over Hypertonic Saline During the First 30 Minutes of Resuscitation Following Hemorrhagic Hypotension in Conscious Swine. -- Wade et al.

INTRODUCTION

Hypertonic saline/dextran solutions (1-4) and hypertonic saline alone (5-8) have been demonstrated to be efficacious in improving cardiovascular function as well as survival when administered after hemorrhagic hypotension. Recently, questions have arisen concerning the superiority of hypertonic saline/dextran over hypertonic saline when administered during the acute period after hemorrhage. The acute period of interest is the first 30 minutes following treatment because it is the average transport time for a trauma victim in the areas of clinical study (9-12). This period is defined as the time between arrival of paramedics at the accident scene and arrival of the patient in the emergency room at the hospital. The data presented here, excerpted from a larger study (4, 13-15), specifically address responses to the administration of either hypertonic saline/dextran or hypertonic saline alone over the first 30 min after treatment. Hypertonic saline/dextran was superior to hypertonic saline alone as a plasma expander, consequently it also elicited superior improvements in cardiovascular function and oxygen delivery.

METHODS

Fourteen immature Yorkshire pigs were used in this portion of the overall study. They were obtained from a commercial breeder and housed in a common indoor laboratory holding facility for one to three weeks prior to experimentation. During this interval and subsequently, the animals were fed a commercial chow (Purina Pig Chow, Ralston Purina Co., St. Louis, MO) and provided water ad libitum. For seven to ten days (3 days before surgery and on days subsequent to recovery from surgery) the pigs were transported to the laboratory and familiarized with the surroundings, personnel and handling procedures. For one hour daily during this period, they were trained to lie quietly in a modified Pavlov sling and to accept a snout respiratory mask.

After an overnight fast, each pig was transported to the operating room and administered a preanesthetic intramuscular injection of 0.8 mg/kg atropine sulfate, 2.2 mg/kg ketamine HCl and 2.2 mg/kg xylazine. Halothane anesthesia was introduced by snout mask and maintained with an endotracheal catheter. A celiotomy was performed, the spleen removed according to standard procedures (16), and a polyvinylidine sideport catheter (17) implanted in the abdominal aorta for blood removal during hemorrhage. The free end of this catheter was tunneled under the skin and exited at the midlumbar region of the back. The animal was then repositioned, and catheters implanted through a neck

incision in the carotid and pulmonary arteries designed to obtain hemodynamic measurements and blood sampling. Catheter placement was confirmed by noting the desired pressure wave form. The free ends of the catheters were tunneled under the skin and exited on the dorsal surface of the neck. The exteriorized ends of all three catheters were fitted with stub adapters, capped with intermittent infusion plugs, and filled with heparinized saline (100 U/ml). Exit sites were protected with Velcro patches (5 cm x 10 cm) sutured to the skin; a hole (2 cm x 10 cm) was cut in the portion next to the skin to provide access. The animal was observed throughout post-operative recovery, then returned to its holding cage and provided food and water.

Seven to ten days after surgical preparation, following an overnight fast, each pig was transported to the laboratory, placed in the sling, and fitted with the snout respiratory mask. The mask was connected with a one-way Rudolph valve and 2.5-cm tubing to a Horizon System metabolic cart for measuring oxygen consumption. The carotid artery catheter was connected to a Statham P23Db transducer by pressure-monitoring injection tubing and three-way stopcocks. Pressure was recorded with a Gould model 2400 recorder. After a period of 30 to 60 min during which the animal rested quietly in the sling and exhibited stable values for oxygen consumption, the experiment began. A progressive fixed-volume hemorrhage was initiated from the abdominal aorta catheter. The hemorrhage schedule was designed to simulate an exponential rate of blood loss as it might occur in a severed artery in an extremity, with the loss stopped mechanically after one hour. Accordingly, successive 7.5 ml/kg increments were drawn continuously, after 9, 19, 31.5, 44, and 60 min. Total blood loss was 37.5 ml/kg. This hemorrhage resulted in profound hypotension. If left untreated, the hemorrhage would have been 100% lethal within 60 min (4). Immediately after the completion of the hemorrhage, the animal was assigned to one of two treatment groups:

Group I: Hypertonic saline: 7.5 % NaCl (N=8; body weight 24.3$\pm$1.1 kg)
Group II: Hypertonic saline/Dextran: 7.5% NaCl in 6% Dextran-70 (N=6; body weight 25.2$\pm$1.7 kg)

The treatment solution was injected as a bolus (4 ml/kg over 1 min) into the pulmonary artery. All functional variables were measured at the end of hemorrhage and then repeated at 5, 15, and 30 min after treatment. At each time point, blood samples (30 ml arterial and 3 ml venous) were collected. Blood gas and acid-base values were obtained immediately after removal of samples, and the remaining blood was partitioned into chilled test tubes and placed in ice water for subsequent analyses.

Blood gases were measured with an Instrumentation Laboratory Model 1303 blood gas analyzer, hemoglobin concentration and oxygen content with an Instrumentation Laboratory cooximeter, Model 282. Cardiac index was calculated by the Fick equation, and heart rate was determined from the pulse pressure tracing. Stroke index, total peripheral resistance, and left ventricular work were calculated from standard formulas. The changes in plasma volume were estimated from hematocrit changes (18) using an assumed initial volume of 67 ml/kg (16) and a correction for red cell volume loss during hemorrhage. Hematocrits were measured by the microcapillary method in duplicate.

To determine the significance of differences between groups, all parametric data were evaluated with two-factor analyses of variance with group treated as a fixed-effects factor and time as a repeated-measures factor, and values obtained at the end of hemorrhage (before treatment) as the co-variate. Significant differences between the mean values were determined by Newman-Keuls tests. Differences at the end of hemorrhage prior to treatment were compared with analysis of variance. Changes were considered significant when $P<0.05$. Values presented in the text are means $\pm$ S.D.

RESULTS

All of the animals treated with hypertonic saline/dextran survived beyond 30 min. All but one of the animals receiving only hypertonic saline survived beyond 30 min. Values for the animal that died at 25 min were not used in the between-group statistical comparisons. At the end of hemorrhage and prior to treatment, there was no statistical difference in any of the measurements of the two groups.

Both treatments expanded plasma volume resulting in a decrease in hematocrit (Fig. 1). Treatment with hypertonic saline/dextran increased plasma volume by 11.8 $\pm$ 0.7 ml/kg (Fig. 1). With hypertonic saline alone, plasma volume was increased by 8.6 $\pm$ 1.0 ml/kg, a value that was significantly ($P<0.05$) less than that induced by hypertonic saline/dextran. The increase in plasma volume after treatment with hypertonic saline/dextran was sustained, whereas 22% of the initial rise induced by hypertonic saline alone was lost at 30 min.

Cardiac index improved to a significantly greater extent 5 min after treatment with hypertonic saline/dextran (104 ml/kg/min), increasing 106% compared to 60% following treatment with hypertonic saline alone, 46 ml/min/kg (Fig. 2). Though cardiac index fell in both groups over the remainder of the 30-min test period, the difference between treatments was

sustained, with the hypertonic saline/dextran group showing statistically significant ($P<0.05$) higher values.

No significant differences in heart rate were observed, either between groups or as a function of time (Fig. 2). Thus, the improvements in cardiac index were attributable to increases in stroke volume index. Stroke volume index was increased by 0.8 ml/beat/kg with hypertonic saline/dextran compared to 0.4 ml/beat/kg after hypertonic saline alone, a significant between-group difference that was sustained over 30 min (Fig. 2).

Mean arterial pressure rose 33 mmHg 5 min after treatment with hypertonic saline/dextran but by only 9 mmHg after treatment with hypertonic saline alone (Fig. 2). This initial difference was statistically significant ($P<0.05$), but in both groups the beneficial effect was not maintained after 15 min.

Both groups showed reductions in peripheral resistance 5 min following treatment, the effect was significantly ($P<0.05$) greater in pigs resuscitated with hypertonic saline/dextran. This group difference persisted over the 30-minute test period (Fig. 2).

Augmented plasma volume and improved cardiovascular function after both treatments led to improved tissue oxygen delivery, but the effect was significantly greater in the pigs that received hypertonic saline/dextran (Fig. 3). Accordingly, oxygen delivery was increased by 61% immediately after treatment with hypertonic saline/dextran but only 33% after hypertonic saline alone. This early beneficial effect, however, was not fully sustained in either group over the remainder of the 30-min experimental period, but remained greater than the values recorded at the end of hemorrhage only in the HSD group. Throughout this period, tissue oxygen delivery values in the pigs receiving hypertonic saline/dextran were significantly greater than those recorded in pigs receiving hypertonic saline alone.

DISCUSSION

The purpose for administration of resuscitation fluid in the field is to expand blood volume to rectify the loss incurred during hemorrhage. The administration rate of Ringer's lactate or isotonic saline is about 1 ml/min/kg (10,11,12,19). Thus, with a transport time of approximately 20 min, the administered volume would be 20 ml/kg. Of this administered volume, less than one third would remain in the vascular compartment (9,20). This small expansion of volume in the field coupled with the time required to insert an intravenous line has led some physicians to adopt the "scoop and run" philosophy which precludes any attempt

to administer fluids (10,11,21). Administration of small volumes (4 ml/kg) of both of the hypertonic solutions used in the present study increased plasma volume by over 9 ml/kg within 5 min of administration. The increase in plasma volume is 37% greater following resuscitation with hypertonic saline/dextran as compared to hypertonic saline alone. Additionally, the increments induced by hypertonic saline/dextran are sustained over 30 minutes, while those with hypertonic saline are not. These findings are similar to those previously reported by Smith et al (3), though in the initial period, while we demonstrate a difference between the two solutions in swine, they could not distinguish a difference in sheep. The administration of hypertonic saline/dextran thus appears to be effective in rapidly expanding plasma volume and is superior to hypertonic saline alone.

The expansion of plasma volume, induced by hypertonic saline/dextran as well as administration of hypertonic saline alone, was associated with improvements in cardiovascular function (cardiac index, stroke index, and peripheral resistance). However, the changes induced by the combination solution are significantly greater than those induced by hypertonic saline alone, both initially and throughout the thirty minute post-treatment period. Smith et al (3) found the response to hypertonic saline/dextran in the acute phase to be similar to hypertonic saline alone in improving cardiovascular function. In their studies with sheep, a significant difference was only noted after thirty minutes. Smith et al (3) and Maningas et al (2) showed that hypertonic saline/dextran produced a sustained improvement in mean arterial pressure. In the present study, mean arterial pressure increased following either solution, but was not sustained. Though the improvement in mean arterial pressure was transient, other indices of cardiovascular function were improved throughout the 30 min period following hypertonic saline/dextran administration.

Due to the improvement in cardiovascular function, there was a net improvement in oxygen delivery with both solutions. The increase was greater following hypertonic saline/dextran administration but with both solutions, the improvements did not return oxygen delivery to control levels. In addition to its effects on oxygen delivery, Hannon et al (13) recently reported a decrease in O_2 demand following the administration of hypertonic saline/dextran. Thus, administration of hypertonic saline/dextran could alleviate some of the adverse metabolic consequences of shock as it increases oxygen delivery and reduces oxygen demand.

SUMMARY

With significant improvements in plasma volume expansion, cardiovascular function, and oxygen delivery, hypertonic saline/dextran is superior to hypertonic saline alone in the first 30 minutes post-treatment in conscious hypovolemic swine. Theoretically, these improvements in the first 30 minutes following the administration of hypertonic saline/dextran could lead to improvements in outcome when compared to hypertonic saline alone.

CONCLUSIONS

1) The increase in plasma volume is 37% greater following resuscitation with hypertonic saline/dextran as compared to hypertonic saline alone. Furthermore, the increments induced by hypertonic saline/dextran are sustained over 30 min, while those of hypertonic saline are not.

2) Improvements in cardiovascular function (cardiac index, stroke index, and peripheral resistance) induced by hypertonic saline/dextran are significantly greater than those induced by hypertonic saline alone, both initially and throughout the 30 min post-treatment period.

3) Hypertonic saline/dextran produces a two-fold improvement in oxygen delivery compared to hypertonic saline alone, a difference that persists for 30 min.

4) Administration of hypertonic saline/dextran following hemorrhagic hypotension is superior to hypertonic saline alone over the first 30 min post-treatment in conscious pigs.

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FIGURE LEGENDS

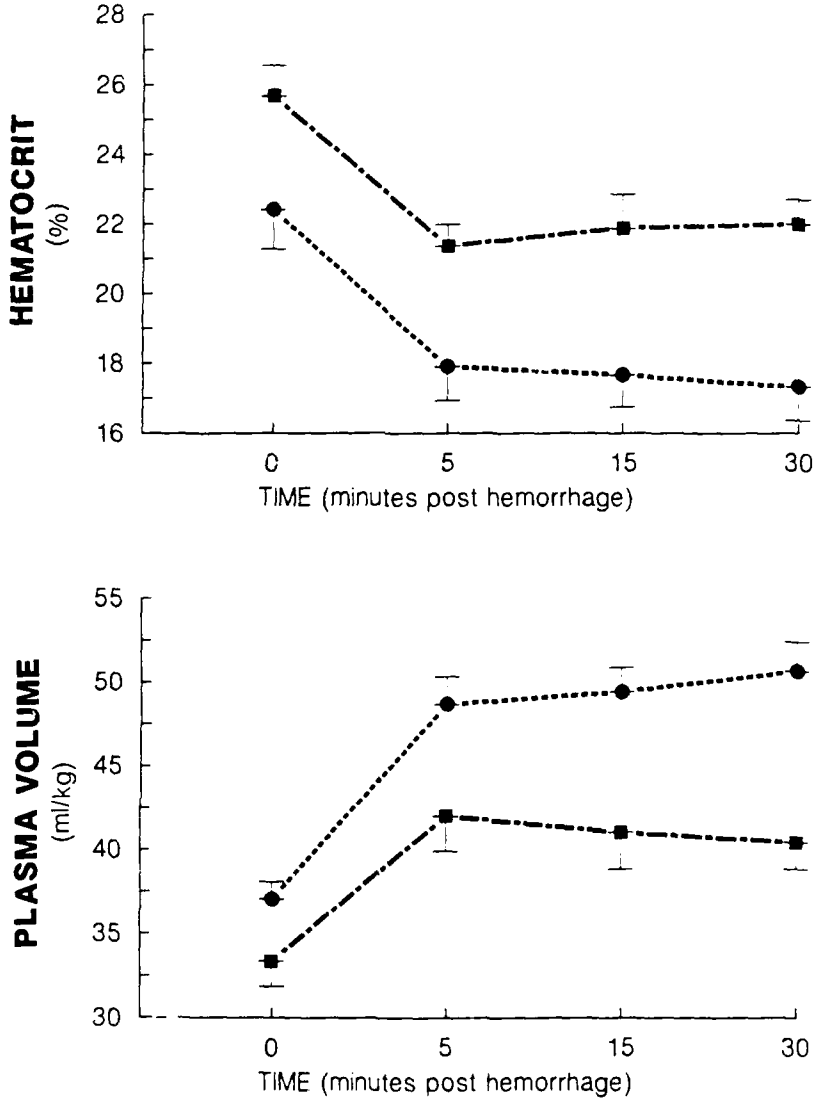

Figure 1: Hematocrit and plasma volume responses to resuscitation following hemorrhage with hypertonic saline/dextran (•---•) or hypertonic saline (■—■) alone.

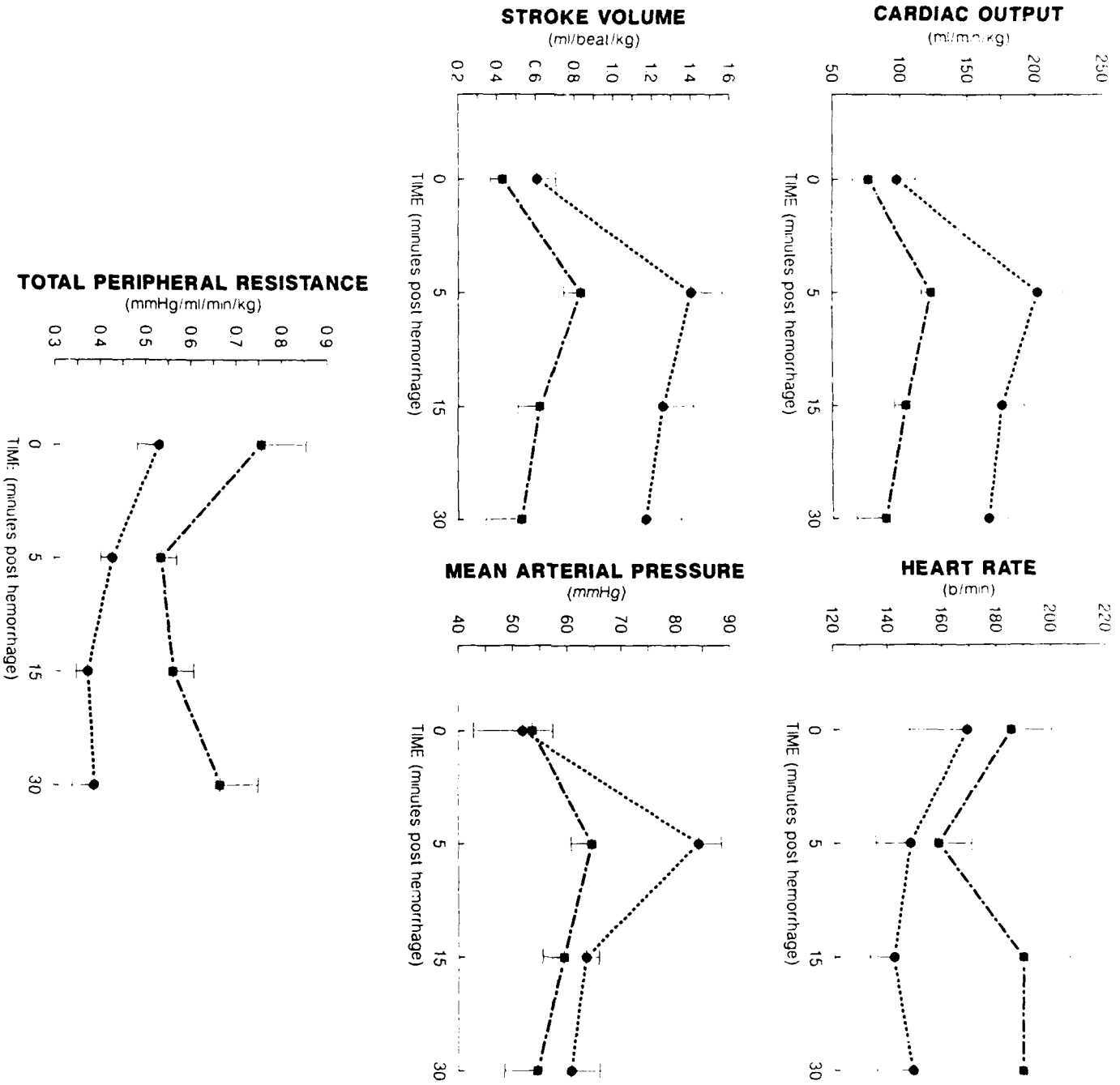

Figure 2: Cardiovascular and hemodynamic responses to resuscitation from hemorrhage with hypertonic saline/dextran (- - -) or hypertonic saline (— —) alone.

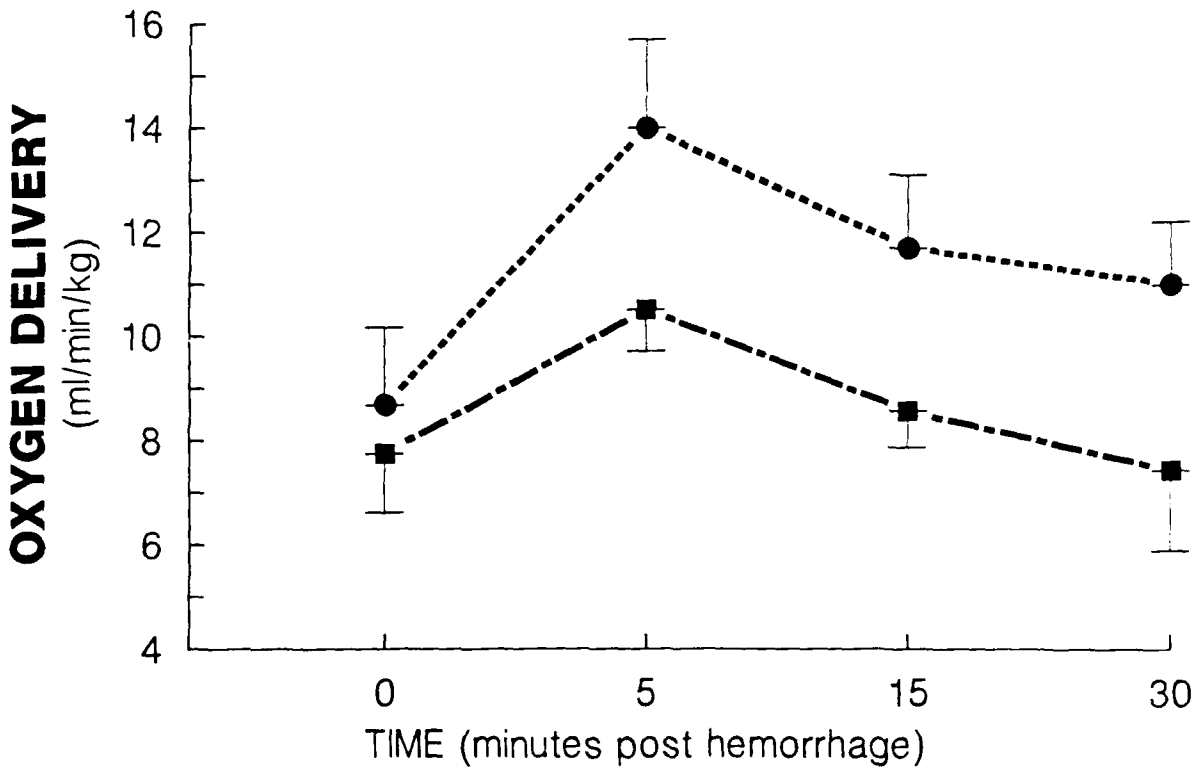

Figure 3: Oxygen delivery in response to resuscitation from hemorrhage with hypertonic saline/dextran (·····) or hypertonic saline (– – –) alone.

APPENDIX 1 RAW DATA

Note-Pig #23 which died at 25 min post treatment with hypertonic saline alone was used in the individual time point calculations, but was not used in the statistical comparisons between groups.

Appendix 1

RAW DATA

HEMATOCRIT
(%)

Animal #	TIME (post hemorrhage) 0 min	5 min	15 min	30 min
GROUP HS				
19	24.0	20.0	19.0	20.0
32	30.5	25.0	28.0	26.5
23	24.0	21.0	20.0	21.0
24	27.0	22.0	21.0	21.0
37	26.0	21.0	22.0	21.0
26	27.0	21.0	23.0	23.0
27	23.0	19.0	20.0	21.5
28	24.0	22.0	22.0	22.0
MEAN	25.69	21.38	21.88	22.00
STDEV	2.46	1.77	2.80	2.02
SEM	0.87	0.62	0.99	0.71
GROUP HSD				
31	24.0	19.0	18.0	18.0
32	24.0	19.0	19.0	18.0
39	24.0	19.0	19.0	20.0
40	17.0	13.5	13.5	13.0
42	22.0	17.0	17.0	18.0
44	23.5	20.0	19.5	17.0
MEAN	22.42	17.92	17.67	17.33
STDEV	2.76	2.38	2.23	2.34
SEM	1.13	0.97	0.91	0.96

RAW DATA

Appendix 1

PLASMA VOLUME
(ml/kg)

	TIME (post hemorrhage)			
Animal #	0 min	5 min	15 min	30 min
GROUP HS				
19	37.7	47.3	50.3	47.2
32	27.3	35.5	30.6	32.9
23	33.4	39.5	41.9	39.5
24	29.3	38.0	40.2	40.2
37	31.5	41.2	38.9	41.2
26	35.5	48.7	43.5	43.5
27	39.9	50.4	47.3	43.3
28	32.2	35.9	35.9	36.0
MEAN	33.35	42.06	41.08	40.48
STDEV	4.21	5.92	6.23	4.520
SEM	1.49	2.09	2.20	1.598
GROUP HSD				
31	35.4	47.2	50.3	50.3
32	37.8	50.4	50.4	53.8
39	36.7	49.0	49.0	46.0
40	41.8	54.5	54.5	56.9
42	36.1	49.2	49.2	46.0
44	34.5	42.1	43.4	51.1
MEAN	37.06	48.74	49.48	50.70
STDEV	2.58	4.06	3.57	4.29
SEM	1.05	1.66	1.46	1.75

Appendix 1

RAW DATA

CARDIAC OUTPUT
(ml/min/kg)

TIME (post hemorrhage)

Animal #	0 MIN	5 MIN	15 MIN	30 MIN
GROUP HS				
19	74	119	99	104
36	45	110	126	61
23	60	111	74	
24	104	144	102	104
37	135	150	129	179
26 *				
27	65	128	121	54
28	54	99	78	32
MEAN	76.7	123.0	104.1	89.0
STDEV	31.8	18.7	22.4	52.6
SEM	12.0	7.1	8.5	21.5
GROUP HSD				
31	94	181	140	130
32	89	159	153	160
39	82	206	177	180
40	48	152	150	129
42	136	252	176	166
44	137	261	253	222
MEAN	97.7	201.8	174.8	164.5
STDEV	34.1	46.5	41.0	34.7
SEM	13.9	19.0	16.8	14.2

* not able to calculate due to co-oximeter failure.

Appendix 1 RAW DATA

HEART RATE
(b/min)

Animal #	TIME (post hemorrhage) 0 MIN	5 MIN	15 MIN	30 MIN
GROUP HS				
19	144	132	144	144
36	114	102	162	210
23	174	168	246	
24	246	204	228	246
37	180	126	108	132
26	198	180	216	146
27	204	180	222	258
28	222	174	190	190
MEAN	185.3	158.3	189.5	189.4
STDEV	42.2	34.4	47.7	50.9
SEM	14.9	12.2	16.9	19.3
GROUP HSD				
31	144	150	126	138
32	126	132	126	126
39	168	114	138	138
40	168	156	156	180
42	270	204	180	198
44	138	132	126	114
MEAN	169.0	148.0	142.0	149.0
STDEV	52.2	31.2	22.0	32.7
SEM	21.3	12.7	9.0	13.4

Appendix 1

RAW DATA

MEAN ARTERIAL PRESSURE
(mmHg)

TIME (post hemorrhage)

Animal #	0 MIN	5 MIN	15 MIN	30 MIN
GROUP HS				
19	48	66	59	60
36	31	60	52	48
23	53	77	56	
24	61	69	69	61
37	58	58	63	63
26	57	63	77	75
27	54	73	59	51
28	67	51	40	24
MEAN	53.6	64.6	59.4	54.6
STDEV	10.7	8.4	11.1	16.1
SEM	3.8	3.0	3.9	6.1
GROUP HSD				
31	49	85	58	63
32	57	81	67	57
39	31	81	62	60
40	28	69	56	59
42	89	100	71	83
44	57	90	67	43
MEAN	51.8	84.3	63.5	60.8
STDEV	22.1	10.3	5.8	12.9
SEM	9.0	4.2	2.4	5.3

-Appendix 1 RAW DATA

STROKE VOLUME
(ml/beat/kg)

TIME (post hemorrhage)

Animal #	0 MIN	5 MIN	15 MIN	30 MIN
GROUP HS				
19	0.51	0.90	0.69	0.72
36	0.39	1.08	0.78	0.29
23	0.34	0.66	0.30	
24	0.42	0.71	0.45	0.42
37	0.75	1.19	1.19	1.36
26 *				
27	0.32	0.71	0.55	0.21
28	0.24	0.57	0.41	0.17
MEAN	0.427	0.831	0.623	0.528
STDEV	0.166	0.232	0.300	0.452
SEM	0.063	0.088	0.113	0.185
GROUP HSD				
31	0.65	1.21	1.11	0.94
32	0.71	1.20	1.21	1.27
39	0.49	1.81	1.28	1.30
40	0.29	0.97	0.96	0.72
42	0.50	1.24	0.98	0.84
44	0.99	1.98	2.01	1.95
MEAN	0.605	1.401	1.259	1.170
STDEV	0.240	0.396	0.388	0.447
SEM	0.098	0.162	0.158	0.183

* not able to calculate due to co-oximeter failure.

Appendix 1

RAW DATA

TOTAL PERIPHERAL RESISTANCE
(mmHg/ml/min/kg)

TIME (post hemorrhage)

Animal #	0 MIN	5 MIN	15 MIN	30 MIN
GROUP HS				
19	0.65	0.55	0.60	0.58
36	0.69	0.55	0.41	0.79
23	0.88	0.69	0.76	
24	0.59	0.48	0.68	0.59
37	0.43	0.39	0.49	0.35
26				
27	0.83	0.57	0.49	0.94
28	1.24	0.52	0.51	0.75
MEAN	0.758	0.535	0.562	0.666
STDEV	0.261	0.093	0.121	0.206
SEM	0.099	0.035	0.046	0.084
GROUP HSD				
31	0.52	0.47	0.41	0.48
32	0.64	0.51	0.44	0.36
39	0.38	0.39	0.35	0.33
40	0.58	0.45	0.37	0.46
42	0.65	0.40	0.40	0.50
44	0.42	0.34	0.26	0.19
MEAN	0.532	0.428	0.374	0.388
STDEV	0.115	0.060	0.062	0.117
SEM	0.047	0.025	0.025	0.048

-Appendix 1 RAW DATA

OXYGEN DELIVERY
(ml/min/kg)

TIME (post hemorrhage)

Animal #	0 MIN	5 MIN	15 MIN	30 MIN
GROUP HS				
19	7.5	10.0	8.2	8.9
36	4.7	10.0	9.6	5.9
23	5.6	8.7	6.1	
24	10.3	12.1	8.4	8.0
37	13.2	14.3	11.3	13.8
26				
27	6.4	10.6	9.8	5.2
28	6.5	8.0	6.6	2.9
MEAN	7.75	10.52	8.57	7.44
STDEV	2.99	2.11	1.85	3.78
SEM	1.13	0.80	0.70	1.54
GROUP HSD				
31	8.5	13.9	10.4	9.5
32	7.4	10.3	10.2	10.4
39	8.0	15.9	13.1	13.5
40	3.1	7.8	7.5	6.5
42	12.9	17.6	11.3	11.3
44	12.2	18.5	17.7	14.9
MEAN	8.68	14.01	11.70	11.00
STDEV	3.57	4.24	3.46	2.99
SEM	1.5	1.7	1.41	1.22

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